SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Fareston 60 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 60 mg toremifene (as citrate).

Excipient with known effect
One tablet contains 28.5 mg of lactose (as monohydrate). For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.

White, round, flat, bevelled edge tablet with TO 60 on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

First line hormone treatment of hormone-dependent metastatic breast cancer in postmenopausal patients.

Fareston is not recommended for patients with estrogen receptor negative tumours.

4.2 Posology and method of administration

Posology

The recommended dose is 60 mg daily.

Renal impairment
No dose adjustment is needed in patients with renal insufficiency.

Hepatic impairment
Toremifene should be used cautiously in patients with liver impairment (see section 5.2).

Paediatric population
There is no relevant use of Fareston in the paediatric population.

Method of administration

Toremifene is administered orally. Toremifene can be taken with or without food.

4.3 Contraindications

- pre-existing endometrial hyperplasia and severe hepatic failure are contra-indications in long-term use of toremifene.
- hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- both in preclinical investigations and in humans, changes in cardiac electrophysiology have been observed following exposure to toremifene, in the form of QT prolongation. For reasons of drug safety, toremifene is therefore contraindicated in patients with:
- congenital or documented acquired QT prolongation
- electrolyte disturbances, particularly in uncorrected hypokalaemia
- clinically relevant bradycardia
- clinically relevant heart failure with reduced left-ventricular ejection fraction
- previous history of symptomatic arrhythmias.

Toremifene should not be used concurrently with other drugs that prolong the QT interval (see also section 4.5).

4.4 Special warnings and precautions for use

Gynaecological examination should be performed before treatment administration, closely looking at pre-existing endometrial abnormality. Afterwards gynaecological examination should be repeated at least once a year. Patients with additional risk of endometrial cancer, e.g. patients suffering from hypertension or diabetes, having high BMI (> 30) or history of hormone replacement therapy should be closely monitored (see also section 4.8).

Anemia, leukopenia and thrombocytopenia have been reported. Red blood cell, leukocyte or platelet counts should be monitored when using Fareston.

Cases of liver injury, including elevation of liver enzymes (> 10 times upper limit of normal), hepatitis and jaundice have been reported with toremifene. Most of them occurred during the first months of treatment. The pattern of the liver damage was predominantly hepatocellular.

Patients with a history of severe thromboembolic disease should generally not be treated with toremifene (see also section 4.8).

Fareston has been shown to prolong the QTc interval on the electrocardiogram in some patients in a dose-related manner. The following information regarding QT-prolongation is of special importance (for contraindications see section 4.3).

A QT clinical study with a 5-arm parallel design (placebo, moxifloxacin 400 mg, toremifene 20 mg, 80 mg, and 300 mg) has been performed in 250 male patients to characterize the effects of toremifene on the QTc interval duration. The results of this study show a clear positive effect of toremifene in the 80 mg group with mean prolongations of 21–26 ms. Regarding the 20 mg group, this effect is significant as well, according to ICH guidelines, with upper confidence interval of 10–12 ms. These results strongly suggest an important dose-dependent effect. As women tend to have a longer baseline QTc interval compared with men, they may be more sensitive to QTc-prolonging medications. Elderly patients may also be more susceptible to drug-associated effects on the QT interval.

Fareston should be used with caution in patients with ongoing proarrhythmic conditions (especially elderly patients) such as acute myocardial ischaemia or QT prolongation as this may lead to an increased risk for ventricular arrhythmias (incl. Torsade de pointes) and cardiac arrest (see also section 4.3).
If signs or symptoms that may be associated with cardiac arrhythmia occur during treatment with Fareston, treatment should be stopped and an ECG should be performed.

If the QTc interval is > 500 ms, Fareston should not be used.

Patients with non-compensated cardiac insufficiency or severe angina pectoris should be closely monitored.

Hypercalcemia may occur at the beginning of toremifene treatment in patients with bone metastasis and thus these patients should be closely monitored.

There are no systematic data available from patients with labile diabetes, from patients with severely altered performance status or from patients with cardiac failure.

Excipients
Fareston tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

This medicinal product contains less than 1 mmol (23 mg) sodium per dosage unit, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

An additive effect on QT interval prolongation between Fareston and the following drugs and other medicinal products that may prolong the QTc interval cannot be excluded. This might lead to an increased risk of ventricular arrhythmias, including Torsade de pointes. Therefore co-administration of Fareston with any of the following medicinal products is contraindicated (see also section 4.3):

- antiarrhythmics class IA (e.g. quinidine, hydroquinidine, disopyramide)
- antiarrhythmics class III (e.g. amiodarone, sotalol, dofetilide, ibutilide)
- neuroleptics (e.g. phenothiazines, pimozide, sertindole, haloperidol, sultopride),
- certain antimicrobials agents (moxifloxacin, erythromycin IV, pentamidine, antimalarials particularly halofantrine)

- certain antihistaminics (terfenadine, astemizole, mizolastine)
- others (cisapride, vincamine IV, bepridil, diphemanil).

Drugs which decrease renal calcium excretion, e.g. thiazide diuretics, may increase the risk of hypercalcaemia.

Enzyme inducers, like phenobarbital, phenytoin and carbamazepine, may increase the rate of toremifene metabolism thus lowering the steady-state concentration in serum. In such cases doubling of the daily dose may be necessary.

There is a known interaction between anti-estrogens and warfarin-type anticoagulants leading to a seriously increased bleeding time. Therefore, the concomitant use of toremifene with such drugs should be avoided.

Theoretically the metabolism of toremifene is inhibited by drugs known to inhibit the CYP3A enzyme system which is reported to be responsible for its main metabolic pathways. Examples of such drugs are antifungal imidazoles (ketoconazole); other antifungal agents (itraconazole, voriconazole, posaconazole); protease inhibitors (ritonavir, nelfinavir), macrolides (clarithromycin, erythromycin, telithromycine). Concomitant use of those drugs with toremifene should be carefully considered.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data from the use of Fareston in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

Fareston should not be used during pregnancy.

Breast-feeding
In rats, decreased body weight gain of the offspring during lactation was observed.

Fareston should not be used during lactation.

Fertility
Toremifene is recommended for postmenopausal patients.

4.7 Effects on ability to drive and use machines

Toremifene has no influence on the ability to drive and use machines.

4.8 Undesirable effects

The most frequent adverse reactions are hot flushes, sweating, uterine bleeding, leukorrhea, fatigue, nausea, rash, itching, dizziness and depression. The reactions are usually mild and mostly due to thehormonal action of toremifene.

The frequencies of the adverse reactions are classified as follows:
Very common (≥ 1/10)
Common (≥ 1/100 to <1/10)
Uncommon (≥ 1/1,000 to < 1/100)
Rare (≥ 1/10 000 to < 1/1 000)
Very rare (< 1/10 000), not known (cannot be estimated from the available data).

System organ class	Very common	Common	Uncommon	Rare	Very rare	Not known
Neoplasms beningn, malignant and unspecified (including cysts and polyps)					Endometrial cancer	
Blood and lymphatic system disorders						Thrombo-cytopenia, anaemia and leukopenia
Metabolism and nutrition disorders			Loss of appetite			Hypertriglyceridaemia
Psychiatric disorders		Depression	Insomnia			
Nervous system disorders		Dizziness	Headache			
Eye disorders					Transient corneal opacity	
Ear and labyrinth disorders				Vertigo		
Vascular disorders	Hot flushes		Thromboembolic events			
Respiratory, thoracic and mediastinal disorders			Dyspnoea			
Gastrointestinal disorders		Nausea, vomiting	Constipation			
Hepatobiliary disorders				Increase of transaminases	Jaundice	Hepatitis, hepatic steatosis
Skin and subcutaneous tissue disorders	Sweating	Rash, itching			Alopecia	
Reproductive system and breast disorders		Uterine bleeding, leukorrhea	Endometrial hypertrophy	Endometrial polyps	Endometrial hyperplasia	

General disorders and administration site conditions		Fatigue, oedema	Weight increase			

Thromboembolic events include deep venous thrombosis, thrombophlebitis and pulmonary embolism (see also section 4.4).

Toremifene treatment has been associated with changes in liver enzyme levels (increases of transaminases) and in very rare occasions with more severe liver function abnormalities (jaundice).

A few cases of hypercalcaemia have been reported in patients with bone metastases at the beginning of toremifene treatment.

Endometrial hypertrophy may develop during the treatment due to the partial estrogenic effect of toremifene. There is a risk of increased endometrial changes including hyperplasia, polyps and cancer. This may be due to the underlying mechanism/estrogenic stimulation (see also section 4.4).
Fareston increases the QT interval in a dose-related manner (see also section 4.4).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Vertigo, headache and dizziness were observed in healthy volunteer studies at daily dose of 680 mg. The dose-related QTc interval prolongation potential of Fareston should also be taken into account in cases of overdose. There is no specific antidote and the treatment is symptomatic.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Endocrine therapy, Anti-estrogens, ATC code: L02BA02

Toremifene is a nonsteroidal triphenylethylene derivative. As other members of this class, e.g. tamoxifen and clomifene, toremifene binds to estrogen receptors and may produce estrogenic, anti-estrogenic or both effects, depending upon the duration of

treatment, animal species, gender, target organ and variable selected. In general, however, nonsteroidal triphenylethylene derivatives are predominantly anti-estrogenic in rats and man and estrogenic in mice.

In post-menopausal breast cancer patients, toremifene treatment is associated with modest reductions in both total serum cholesterol and low density lipoprotein (LDL).

Toremifene binds specifically to estrogen receptors, competitively with oestradiol, and inhibits estrogen-induced stimulation of DNA synthesis and cell replication. In some experimental cancers and/or using high-dose, toremifene displays anti-tumour effects which are not estrogen-dependent.

The anti-tumour effect of toremifene in breast cancer is mainly due to the anti-estrogenic effect, although other mechanisms (changes in oncogene expression, growth factor secretion, induction of apoptosis and influence on cell cycle kinetics) may also be involved in the anti-tumour effect.

5.2 Pharmacokinetic properties

Absorption
Toremifene is readily absorbed after oral administration. Peak concentrations in serum are obtained within 3 (range 2–5) hours. Food intake has no effect on the extent of absorption but may delay the peak concentrations by 1.5–2 hours. The changes due to food intake are not clinically significant.

Distribution
The serum concentration curve can be described by a biexponential equation. The half-life of the first (distribution) phase is 4 (range 2–12) hours, and of the second (elimination) phase 5 (range 2–10) days. The basal disposition parameters (CL and V) could not be estimated due to the lack of intravenous study. Toremifene binds extensively (> 99.5%) to serum proteins, mainly to albumin. Toremifene obeys linear serum kinetics at oral daily doses between 11 and 680 mg. The mean concentration of toremifene at steady-state is 0.9 (range 0.6–1.3) µg/ml at the recommended dose of 60 mg per day.

Biotransformation
Toremifene is extensively metabolised. In human serum the main metabolite is N-demethyltoremifene with mean half-life of 11 (range 4–20) days. Its steady-state concentrations are about twice compared to those of the parent compound. It has similar anti-estrogenic, albeit weaker anti-tumour activity than the parent compound.

It is bound to plasma proteins even more extensively than toremifene, the protein bound fraction being > 99.9%. Three minor metabolites have been detected in human serum: (deaminohydroxy)toremifene, 4-hydroxytoremifene, and N,N-didemethyltoremifene. Although they have theoretically interesting hormonal effects, their concentrations during toremifene treatment are too low to have any major biological importance.

Elimination

Toremifene is eliminated mainly as metabolites to the faeces. Enterohepatic circulation can be expected. About 10% of the administered dose is eliminated via urine as metabolites. Owing to the slow elimination, steady-state concentrations in serum are reached in 4 to 6 weeks.

Characteristics in patients
Clinical anti-tumour efficacy and serum concentrations have no positive correlation at the recommended daily dose of 60 mg.

No information is available concerning polymorphic metabolism. Enzyme complex, known to be responsible for the metabolism of toremifene in humans, is cytochrome P450-dependent hepatic mixed function oxidase. The main metabolic pathway, N-demethylation, is mediated mainly by CYP3A.

Pharmacokinetics of toremifene were investigated in an open study with four parallel groups of ten subjects: normal subjects, patients with impaired (mean AST 57 U/L - mean ALT 76 U/L - mean gamma GT 329 U/L) or activated liver function (mean AST 25 U/L - mean ALT 30 U/L - mean gamma GT 91 U/L - patients treated with antiepileptics) and patients with impaired renal function (creatinine: 176 µmol/L). In this study the kinetics of toremifene in patients with impaired renal function were not significantly altered as compared to normal subjects. The elimination of toremifene and its metabolites was significantly increased in patients with activated liver function and decreased in patients with impaired liver function.

5.3 Preclinical safety data

The acute toxicity of toremifene is low with LD-50 in rats and mice of more than 2 000 mg/kg. In repeated toxicity studies the cause of death in rats is gastric dilatation. In the acute and chronic toxicity studies most of the findings are related to the hormonal effects of toremifene. The other findings are not toxicologically significant. Toremifene has not shown any genotoxicity and has not been found to be carcinogenic in rats. In mice, estrogens induce ovarian and testicular tumours as well as hyperostosis and osteosarcomas. Toremifene has a species-specific estrogen-like effect in mice and causes similar tumours. These findings are postulated to be of little relevance for the safety in man, where toremifene acts mainly as an anti-estrogen.

Non clinical *in vitro* and *in vivo* studies have evidenced the potential of toremifene and its metabolite to prolong cardiac repolarisation and this can be attributed to the blockade of hERG channels.

In vivo, high plasma concentrations in monkeys caused a 24% prolongation in QTc, which is in line with QTc findings in humans.

It is also to be noted that the C_{max} observed in the monkeys (1 800 ng/ml) is two-fold compared to the mean C_{max} observed in humans at a daily dose of 60 mg.

Action potential studies in isolated rabbit heart have shown that toremifene induce cardiac electrophysiological changes which start to develop at concentrations approximately 10 fold compared to the calculated free therapeutic plasma concentration in human.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maize starch
Lactose monohydrate
Povidone
Sodium starch glycolate
Magnesium stearate
Cellulose, microcrystalline
Silica, colloidal anhydrous.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Green PVC foil and aluminium foil blister in a cardboard box.

Package sizes: 30 and 100 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Orion Corporation
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FI-02200 Espoo
Finland

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 27925/0106

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

01/01/2021

10 DATE OF REVISION OF THE TEXT

14/08/2024